DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 20, 2011 has been entered.

Election/Restrictions

2. New claim 76 is a method claim that lacks an active step and thus is not considered to be statutory under 35 USC §§ 101 and 112, second paragraph. In the restriction requirement mailed August 9, 2007, group III drawn to compositions was restricted from methods of preparing and methods of treating wherein the sustained release dosage form was administered. Due to the lack of active step, it is unclear to which of the two method groups new claim 76 belongs, but either way, the claim has been withdrawn from consideration as not drawn to the subject matter of the elected group.

Response to Amendment

3. The declaration under 37 CFR 1.132 filed May 10, 2012 is insufficient to overcome the rejection of the pending claim based upon Shell and Seroff, optionally further in view of Tobyn et al. as set forth in the last Office action because: many of the features discussed are not present as limitation in the instant claims and the statements contradicting the teachings of the applied art are not supported by additional evidence or discussion. Applicants state that many workers in the field would not term HPMC to be a swellable polymer (¶ 6). This directly contradicts Shell et al. which states several times that "the water-swellable polymer ... is any polymer that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of an incorporated drug. Examples of polymers ... are ...cellulose polymers and their derivatives" (col 7, ln 54 – 60) and HPMC is exemplified at col 8, ln 16 as such a cellulose polymer. While this may not be a universally accepted definition, nothing in declaration indicates why workers in the field would not agree with the statements of Shell et al. It is also noted that to some extent the remarks in declaration are contradicted by the argument of counsel (p 10, ¶ 2) indicating that HPMC, MCC and SMCC may be water swellable. In response to applicant's argument that they had the cellulose to act as a tableting aid and maltodextrin as glue, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter.

1985). It is also noted that Seroff et al. discloses the use of maltodextrin as a binder for use in tableting of the drug layer (col 21, ln 50 – 53), in line with applicants description of maltodextrin as a glue. The patentability of a composition is determined by the ingredients which are present and not the particular reason for adding a particular ingredient. As such, the reasons set forth in the rejection for adding a particular ingredient need not be the same rationale as to why the inventor added that ingredient. It is noted that the features upon which applicant relies (i.e., that the dosage from does not rely on an osmotic gradient, or swelling on imbibition of water to control the rate of release and is not an osmotic pump) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 112 – 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 75 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. While starch and celluloses are both comprised of glucose repeating units, celluloses have beta linkages connecting the repeating units while starches have an alpha linkage connecting the glucose monomer repeating units. The

Markush group of claim 75 of water insoluble or partially water insoluble celluloses includes starch. It is therefore unclear if applicant wished to defined "cellulose" to include starches as well as celluloses so the metes and bounds of the claim cannot be determined. Please clarify.

Claim Rejections - 35 USC § 112 – 4th Paragraph

6. The following is a quotation of the fourth paragraph of 35 U.S.C. 112:

> Subject to the [fifth paragraph of 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

7. Claim 46 is rejected under 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. While starch and celluloses are both comprised of glucose repeating units, celluloses have beta linkages connecting the repeating units while starches have an alpha linkage connecting the glucose monomer repeating units. Therefore, starches are not celluloses and the inclusion of starch broadens the claim beyond the subject matter of the parent claims, which was limited to glucose polymers with beta linkages. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 38, 40 – 47, 54 – 56, 59, 60 and 71 – 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shell et al. (US 6,340,475) in view of Seroff et al. (US 6,387,403). This rejection is MAINTAINED for the reasons set forth herein.

Shell et al. discloses compositions wherein drug release is accomplished by the imbibition of water by hydrophilic polymers (abstract). The formulations take the form of particles, tablets or particles retained in capsules (col 9, ln 61 – 62), all of which read on solid oral dosage forms. The water-swellable polymers can be a variety of materials, including a variety of celluloses, including microcrystalline cellulose, starch and starch-based polymers (col 7, ln 62 and 65 - 66), and the cellulose polymers hydroxymethyl-

cellulose, hydroxyethyl cellulose, HPMC and carboxymethyl cellulose (col 8, ln 15 – 17). Both hydroxy ethylcellulose and HPMC are particularly preferred as the cellulose polymer (col 8, ln 23 – 25). While water-swellable polymers can be used individually, certain combination will often provide a more controlled release of the drug than their components individually (col 9, ln 41 – 50). Examples given include celluloses such as hydroxyethyl cellulose or hydroxypropyl cellulose in combination with gums such as xanthan gum (col 9, ln 45 – 47). Drug, polymer and stearate are compressed into pellets (col 12, ln 17 – 18), which reads on the mixture in the core required by the instant claims. For example, in example 6 the samples represented by open triangles are a combination of hydroxyethylcellulose (a cellulose ether) and xanthan gum (1:1 ratio; col 15, ln 16 – 21) and are prepared by compression of the listed ingredients into pellets. Among the drugs that are highly water soluble which would benefit from being released in a controlled manner is metformin hydrochloride (col 7, ln 39 – 41).

Shell et al. does not disclose the inclusion of maltodextrin in the composition.

Seroff et al. discloses dosage forms in which a drug is mixed with excipients that provide an osmotic activity gradient that drives fluid from the external environment to form a deliverable drug formulation by imbibition of fluid (col 7, ln 56 – 62). In addition to a drug carrier, osmotically active agents ("osmagents"), lubricants and binders can also be included (col 7, ln 62 – 66). A layer generally comprising one or more osmopolymers and osmagent occurs swells as fluid is imbibed, leading to drug release (col 8, ln 20 – 25). Poly(alkylene) oxides, poly(carboxymethyl celluloses), poly (alkali carboxymethyl celluloses) or hydroxypropylalkyl celluloses such as HPMC can be used as the

hydrophilic polymer (col 13, ln 5 – 32). Polymers that swell will not dissolve in water or an aqueous fluid. Carbohydrates such as maltodextrin can be used alone or in combination with other osmagents (col 13, ln 33 – 37).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate the osmagent maltodextrin into the drug delivery compositions of Shell et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because both Shell et al. and Seroff et al. teach drug delivery devices that are driven by the imbibition of water from the external environment into the drug delivery device. While Shell et al. does not explicitly state that the composition is homogenous, mixing of the various ingredients present in the formulation to homogeneity will decrease the variability in drug dosage amount from one dosage form to the next.

The amount of swelling, determined by the particular polymer(s) and other osmagents such as maltodextrin present in the dosage form will determine the rate and amount of swelling of the dosage form and thus the release rate of the drug from the dosage form. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results of the desired release rate for the particular drug, such as metformin, being released from a given dosage form.

The combination of swellable polymers is taught by the formulations of Seroff and the combination of gums and celluloses is taught as a particularly advantageous combination by Shell et al. to provide more control over the release of drug. The inclusion of maltodextrin also acts to control the imbibition of water and thus control of the drug release rate.

In regards to the claim limitation "wherein said water insoluble or partially water insoluble cellulose in combination with maltodextrin further affects the release of the drug", this is a property of the dosage form. There is no evidence currently on the record that a monolithic, single layer drug delivery form like that taught by Shell et al. will not have this property. "As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." **MPEP 2113** It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Applicants traverse this rejection on the grounds that the inventive compositions are homogenous and that the function of the cellulose ingredient in the instant invention is not the same as in the applied art.

This argument is unpersuasive. Along the lines of the declaration set forth above in which the reason for adding a particular ingredient between the invention and applied prior art need not be the same and the features upon which applicant is relying are not recited in the instant claims. The patentability of a composition is determined by the ingredients which are present and not the particular reason for adding a particular ingredient.

Applicant also argues that Shell does not disclose both the water insoluble or partially water soluble cellulose and sustained release carrier in the same composition as claim 1 only refers to a single polymeric matric. Since Shell does not disclose two allegedly water soluble polymers, the combination of Shell with Seroff does not encompass each element of the claimed invention. Shell alone cannot support an obviousness rejection as the use of maltodextrin is not disclosed. Seroff alone does not render obvious or anticipate the claims since the maltodextrin is not mixed with any of the cellulose polymers. Applicants have discovered that maltodextrin counteracts the increase in release rate caused by the cellulose ingredient and the water-swellability of the sustained release carrier is not a limiting factor.

These arguments are unpersuasive. The instant claims are met when any material reading on a sustained release carrier, in combination with a drug, maltodextrin and a cellulose as required by the instant claims are homogenously mixed (this does not apply when a particular composition is required for the sustained release carrier in some of the dependent claims, wherein the claim limitations would be met when a water insoluble or partially water insoluble cellulose other than HPMC was included in the

composition). Shell et al. discloses that a sustained release carrier can be a cellulose. The documents are prior art for all that they disclose and the disclosure is not limited to the claims so the teaching of claim 1 of a polymeric matrix, that can comprise multiple ingredients although not explicitly recited in claim 1, does not render the claims obvious.

11. Claims 38, 40 – 48, 54 – 56, 59, 60 and 71 – 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shell et al. and Seroff et al. further in view of Tobyn et al. (Intl J Pharm 1998).

Shell et al. and Seroff et al. are discussed above.

Neither reference discloses the use of silicified microcrystalline cellulose (SMCC).

Tobyn et al. discloses the MCC is widely used as a filler and binder for wet granulation, direct compression tabletting and a filler for hard gelatin capsules (p 183, col 1, ¶1) and it has been rated as the most useful filler for direct compression tabletting (p 183, col 2, ¶1). While MCC is very useful, SMCC possesses a number of advantages in terms of powder flow, tablet strength, lubricant sensitivity and wet granulation (p 184, col 2, ¶ 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate SMCC in place of MCC into the formulations of Shell et al. and Seroff et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Tobyn et al. teaches the improved behavior of SMCC when formulations are prepared.

Microcrystalline cellulose is commonly used in tablets as a filler and binder for wet granulation, direct compression tableting and would the use of SMCC would provide those benefits as well as the enhanced properties provided by using the silicified form of MCC in the table.

Applicants traverse this rejection on the grounds that Tobyn does not address the inadequacies of Shell and Seroff. As discussed above, Shell and Seroff are not deficient so Tobyn is not required to address those inadequacies and further motivates the inclusion of SMCC as filler and binder in tablet formulations, motivating the inclusion of SMCC in addition to the cellulose materials found in the sustained release matrix taught by Shell et al.

12. Claims 38, 40 – 47, 54 – 56, 59, 60 and 71 – 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shell et al. (US 6,340,475) in view of Zhou et al. (Int J Pharm, 1996).

Shell et al. is discussed above.

Shell et al. does not disclose the inclusion of maltodextrin in the composition.

Zhou et al. discloses the sustained release of drugs (model drugs included ibuprofen and sodium salicylate) from a matrix of microcrystalline waxes, pregelatinized starches and hydrolyzed starches (abstract). The pellets use a molten hydrophobic component as a binder in combination with a starch derivative (p 156, col 1, ¶ 2) although other materials such as ethyl cellulose and sodium carboxymethyl cellulose

have been used as release-retarding agents in matrix pellets (p 155, col 2, p 1466, col 1, ¶ 1). Corn starch as the pregelatinized starch and maltodextrin as the hydrolyzed starch derivative were used in the examples (p 156, section 2.1). Dosage forms made with DDWCS (corn starch) delayed ibuprofen release and the release could be adjusted by varying the type and concentration of wax (p 158, col 1, ¶ 1). For a dosage form containing 30% LUNACERA® M and ibuprofen, the dosage form with DDWCS released 50% of the drug at 2 hours, with 85% being released after 8 hours but when WMD (maltodextrin) was used instead of corn starch with the same amount of LUNACERA® M, 50% of the drug was released at 12 hours, and 95% of the drug released after 48 hours, demonstrating the dramatic influence of maltodextrin to retard drug release (p 158, col 1, ¶ 1 and col 2, ¶ 2).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate maltodextrin into the drug delivery compositions of Shell et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Shell et al. discloses that a variety of polymers can be used as the sustained release carrier, and Zhou et al. demonstrates that maltodextrin can dramatically delay drug release in comparison to starch. By using a mixture of materials that act to sustain drug release, the desired release profile can be obtained by the use of materials having different sustained release effects (e.g., HPMC and maltodextrin). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine

practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results of the desired release rate for the particular drug, such as metformin, being released from a given dosage form. The combination of gums and celluloses is taught as a particularly advantageous combination by Shell et al. to provide more control over the release of drug wherein maltodextrin will also acts to control the drug release rate.

13. Claims 38, 40 – 47, 54 – 56, 59, 60 and 71 – 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shell et al. and Zhou et al. as applied to claims 38, 40 – 47, 54 – 56, 59, 60 and 71 – 75 above, and further in view of Tobyn et al. (Intl J Pharm 1998).

Shell et al. and Zhou et al. are discussed above.

Neither reference discloses the use of silicified microcrystalline cellulose (SMCC).

Tobyn et al. discloses the MCC is widely used as a filler and binder for wet granulation, direct compression tabletting and a filler for hard gelatin capsules (p 183, col 1, ¶1) and it has been rated as the most useful filler for direct compression tabletting (p 183, col 2, ¶1). While MCC is very useful, SMCC possesses a number of advantages in terms of powder flow, tablet strength, lubricant sensitivity and wet granulation (p 184, col 2, ¶ 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate SMCC in place of MCC into the formulations of Shell et al. and Zhou et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Tobyn et al. teaches the improved behavior of SMCC when formulations are prepared. Microcrystalline cellulose is commonly used in tablets as a filler and binder for wet granulation, direct compression tableting and would the use of SMCC would provide those benefits as well as the enhanced properties provided by using the silicified form of MCC in the table.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NISSA WESTERBERG whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Primary Examiner, Art Unit 1618